# Early-life supplementation of vitamins A and D, in water-soluble form or in peanut oil, and allergic diseases during childhood

Inger Kull, RN, PhD,[a,b,d] Anna Bergström, PhD,[b] Erik Melén, MD, PhD,[b,d] Gunnar Lilja, PhD, MD,[c] Marianne van Hage, MD, PhD,[e] Göran Pershagen, PhD, MD,[a,b] and Magnus Wickman, PhD, MD[a,b,d] *Stockholm, Sweden*

**Background: Early vitamin supplementation is given routinely to infants in many countries, but it is unclear whether this affects the risk of allergic diseases.**
**Objectives: We sought to study the association between early-life supplementation of vitamins A and D in water-soluble form or in peanut oil and allergic diseases up to 4 years of age.**
**Methods: A prospective birth cohort of 4089 newborn infants was followed for 4 years using parental questionnaires repeatedly to collect information on exposure and health. At 4 years, the response rate was 90%, and allergen-specific IgE levels to food and airborne allergens were measured in 2614 of the participating children.**
**Results: Vitamins A and D were given to 98% of the children in infancy, and vitamins based in peanut oil dominated (90%). Children supplemented with vitamins A and D in water-soluble form during the first year of life had an almost 2-fold increased risk of asthma (adjusted odds ratio [OD], 2.18; 95% CI, 1.45-3.28), food hypersensitivity (adjusted OR, 1.89; 95% CI, 1.33-2.65), and sensitization to common food and airborne allergens (adjusted OR, 1.88; 95% CI, 1.34-2.64) at age 4 years compared with those receiving vitamins in peanut oil. No increased risk of IgE antibodies to peanut was seen in children receiving vitamins in peanut oil.**
**Conclusion: Supplementation of vitamins A and D in water-soluble form seems to increase the risk of allergic disease up to the age of 4 years compared with supplementation with the same vitamins given in peanut oil.**
**Clinical implications: Vitamins A and D in oil does not seem to increase the risk of allergic disease during childhood. (J Allergy Clin Immunol 2006;118:1299-304.)**

***Key words:*** *Allergic disease, asthma, BAMSE, childhood, fatty acids, prevention, sensitization, vitamin D*

Dietary intake has been suggested to exert protective, as well as unfavorable, effects on asthma and allergic diseases. In recent years there has been a focus on the role of vitamins, antioxidants, fruits, and vegetables, as well as fatty acids.[1-4] For example, early multivitamin supplementation has been reported to increase the risk of asthma and food allergy.[5] High serum levels of vitamin A have been associated with an increased risk of IgE sensitization, and dietary vitamin D supplementation early in life has been associated with atopy and allergic rhinitis in adulthood.[6,7] A possible explanation for these findings is that such vitamins might skew the immune system toward a $T_H2$ response.[8] Accordingly, vitamin D supplementation during infancy has been associated with a reduced risk of type 1 diabetes.[9]

Recommendations about supplementation with vitamins during early childhood are given in many western countries.[10] In Sweden all infants are recommended a dose of 1000 IE of vitamin A and 400 IE of vitamin D daily from 2 weeks of age up to 5 years of age to prevent vitamin A and D deficiency.[11] The vitamins are free of charge during the first 2 years of life and distributed by the Child Health Care units. After the first year of life, the vitamins are recommended to be given during wintertime only. The vitamins can either be water soluble or oil based. At the time of the study, the oil used was refined peanut oil. In general, the oil-based vitamins were recommended because such preparations do not need to be kept cold.

Peanut oil contains omega-6 fatty acids but also a small amount of omega-3 fatty acids.[12,13] A diet rich in omega-3 fatty acids has been suggested to reduce the risk of several autoimmune diseases, and protective effects have been reported also for allergic diseases.[14,15] The use of peanut oil in medications and formulas has been associated with an increased risk of sensitization to peanut in some studies, but data are inconclusive.[16-18]

The primary aim of the present study was to investigate the association between early supplementation of vitamins

From [a]the Department of Occupational and Environmental Health, Stockholm County Council; [b]the National Institute of Environmental Medicine, Karolinska Institutet; [c]Sachs' Children's Hospital, Institute of Södersjukhuset, Karolinska Institutet; [d]the Centre for Allergy Research, Karolinska Institutet; and [e]the Clinical Immunology and Allergy Unit, Department of Medicine, Karolinska Institutet and University Hospital.

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Reprint requests: Inger Kull, RN, PhD, Department of Occupational and Environmental Health, Norrbacka, SE-171 76 Stockholm, Sweden. E-mail: inger.kull@sll.se.

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*Abbreviations used*
BAMSE: Children, Allergy, Milieu, Stockholm, Epidemiological survey
OR: Odds ratio

A and D in water-soluble form or based in peanut oil and development of allergic disease up to the age of 4 years.

## METHODS

### Study design

All newborns in a predefined area of Stockholm, Sweden, were invited to participate in a prospective study (the Children, Allergy, Milieu, Stockholm, Epidemiological survey [BAMSE]) from February 1994 until November 1996. In total, 4089 newborn infants were included, which comprised 75% of all infants born in this area. The study design has been described in detail elsewhere.[19,20] Data on parental allergy and various exposures were obtained by using parental questionnaires when the infants were newborns (median age, 2 months). At 1, 2, and 4 years of age, the parents answered questionnaires with a focus on symptoms related to allergic diseases in their children, as well as on key exposures and possible confounding factors. Data about breast-feeding, diet, and vitamin supplementation were collected from the 1-year questionnaire. The response rates for the questionnaires were 96%, 94%, and 91%, respectively. The information on supplementation with vitamins A and D was provided in 4 predefined categories (vitamins based in peanut oil, vitamins in water-soluble form, vitamins as a combination of the 2 preparations, and no vitamins).

All children with answered questionnaires (n = 3670) at age 4 years were invited to a clinical investigation, including blood sampling. A total of 2965 children agreed to participate, and blood samples were collected from 2614 children. Permission for the study was obtained from the Ethics Committee of Karolinska Institutet, Stockholm.

### Definition of health outcomes

During the first 2 years of life, *asthma* was defined as at least 3 episodes of wheezing in addition to respiratory symptoms treated with inhaled steroids or signs of bronchial hyperreactivity, such as coughing and wheezing during play or physical strain, without ongoing upper respiratory tract infection. At 4 years of age, asthma was defined as at least 4 episodes of wheezing during the last 12 months or at least 1 episode of wheezing during the same period if the child was taking inhaled steroids.[20]

*Eczema* was defined as dry skin in combination with itchy rash for at least 2 weeks with typical localization during the last 12 months, a physician's diagnosis of eczema during the last 24 months, or both.[21]

*Allergic rhinitis* was defined as sneezing, runny or blocked nose, and/or red itchy eyes after exposure to pollen or pets; a physician's diagnosis of allergic rhinitis during the last 24 months; or both.

*Hypersensitivity to food* was defined as specific symptoms (ie, atopic dermatitis, urticaria, edema of the lips/eyes, pruritus around the eyes or runny nose, and asthma) after ingestion of common types of food during the last 24 months.

The terms *transient*, *late-onset*, and *persistent disease* were used to assess onset and duration of disease (asthma, eczema, allergic rhinitis, and food hypersensitivity). *Transient disease* denotes children fulfilling the outcome criteria during the first 2 years of life but not later. *Persistent disease* implies that the child fulfilled the outcome criteria both during the first 2 years of life and at 4 years of age. *Late-onset disease* denotes that the child only fulfilled disease criteria at age 4 years.

The term *multiple diseases* was defined as at least 2 of the following 3 diseases at the age of 4 years: asthma, eczema, or allergic rhinitis.

For *sensitization*, IgE antibodies against a mixture of common inhalant allergens (cat, dog, horse, birch, timothy, mugwort, *Dermatophagoides pteronyssinus*, and *Cladosporium* species) and common food allergens (cow's milk, hen's egg, cod fish, soy bean, peanut, and wheat) were analyzed with Phadiatop and fx5, respectively. Single allergens were analyzed if Phadiatop or fx5 test results were positive ($\geq$0.35 $kU_A/L$; Pharmacia CAP System, Phadia AB, Uppsala, Sweden). Data of the 7 most common single allergens (milk, egg white, peanut, birch, timothy, cat, and horse) are presented here.[22]

### Statistical methods

Difference in the distribution of selected characteristics among the 4 groups (vitamins in peanut oil, vitamins in water-soluble form, both preparations, and no vitamins A and D) was tested with the $\chi^2$ test. The association between vitamin A and D supplementation and the selected health outcomes was analyzed with logistic regression. The results are presented as adjusted odds ratios (ORs) with 95% CIs. Several models were tested to identify potential confounders, and finally, the logistic regression model was adjusted for parental allergic disease (defined as physician-diagnosed asthma, hay fever, or both in combination with allergy to furred pets or pollen in 1 or both parents), maternal age (<25 years, $\geq$25 years), maternal smoking (yes, no), breast-feeding (<4 months, $\geq$4 months), and fish consumption ($\leq$once a month, $\geq$2-3 times a month) because these covariates were associated with both exposure and health outcomes. Other models were also evaluated, such as a broader definition of heredity, also including eczema among the parents and any allergic disease (asthma, eczema, allergic rhinitis, or allergy to pollen or pets) among older siblings, as well as gestational age, damp housing, and socioeconomic status, but these covariates had a small effect on the risk estimates (<3%).

The Wald test was used to assess interaction between covariates (departure from a multiplicative model). All statistical analyses were performed with STATA Statistical Software (release 8.0; StataCorp, College Station, Tex). Complete information on vitamin A and D consumption at age 1 year and answers on all 4 questionnaires were required for inclusion in the analyses. In total, 3618 (88.5%) children fulfilled these criteria.

## RESULTS

Most children (98%) had been given vitamins A and D during the first year of life, and vitamins based in peanut oil dominated (90%). Two hundred thirty-seven (7%) children had received vitamins in water-soluble form, and 73 (2%) had used both alternatives. Only 59 (<2%) children were not given vitamins A and D during the first year of life. The distribution of selected exposure characteristics in relation to supplementation with vitamins A and D is shown in Table I. Some differences were seen among the 4 exposure groups in relation to heredity for allergic disease, maternal smoking, breast-feeding, and fish consumption. Children receiving vitamins A and D in water-soluble form were more exposed to maternal smoking (19% vs 13%, $P = .01$), breast-fed less than 4 months (27% vs 20%, $P = .004$), and had less regular consumption of fish at the age of 1 year (31% vs 19%, $P < .001$)